Piperidine derivates for the treatment of chemokines mediated disease

The present invention concerns piperidine derivatives having pharmaceutical activity, to processes for preparing such derivatives, to pharmaceutical compositions comprising such derivatives and to the use of such derivatives as active therapeutic agents.

Pharmaceutically active piperidine derivatives are disclosed in WO99/38514, WO99/04794 and WO00/35877.

Histamine is a basic amine, 2-(4-imidazolyl)-ethylamine, and is formed from histidine by histidine decarboxylase. It is found in most tissues of the body, but is present in high concentrations in the lung, skin and in the gastrointestinal tract. At the cellular level inflammatory cells such as mast cells and basophils store large amounts of histamine. It is recognised that the degranulation of mast cells and basophils and the subsequent release of histamine is a fundamental mechanism responsible for the clinical manifestation of an allergic process. Histamine produces its actions by an effect on specific histamine G-protein coupled receptors, which are of three main types, H1, H2 and H3. Histamine H1 antagonists comprise the largest class of medications used in the treatment of patients with allergic disorders, for example rhinitis and urticaria. H1 antagonists are useful in controlling the allergic response by for example blocking the action of histamine on post-capillary venule smooth muscle, resulting in decreased vascular permeability, exudation and oedema. The antagonists also produce blockade of the actions of histamine on the H1 receptors on c-type nociceptive nerve fibres, resulting in decreased itching and sneezing.

Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T cells, eosinophils, basophils and neutrophils to sites of inflammation and also play a rôle in the maturation of cells of the immune system. Chemokines play an important rôle in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C, or α) and Cys-Cys (C-C, or β) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

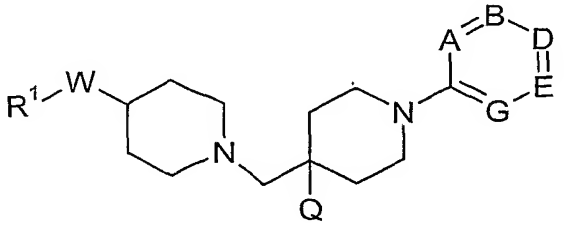
The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β).

Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

Viral infections are known to cause lung inflammation. It has been shown experimentally that the common cold increases mucosal output of eotaxin in the airways. Instillation of eotaxin into the nose can mimic some of the signs and symptoms of a common cold. (See, Greiff L *et al* Allergy (1999) 54(11) 1204-8 [Experimental common cold increase mucosal output of eotaxin in atopic individuals] and Kawaguchi M *et al* Int. Arch. Allergy Immunol. (2000) 122 S1 44 [Expression of eotaxin by normal airway epithelial cells after virus A infection].)

The present invention provides a compound of formula (I):



(I)

wherein:

one of A, B, D, E and G is $CXYCO_2R^5$, another is CH or N and the others are CR^2, CR^3 and CR^4;

Q is hydrogen or hydroxy;

W is CH_2, O, NH or $N(C_{1-4}$ alkyl);

X is O or a bond;

Y is $CR^{10}R^{11}$, $CR^{10}R^{11}CR^{12}R^{13}$, $CR^{10}R^{11}CR^{12}R^{13}CR^{14}R^{15}$;

R^1 is phenyl optionally substituted by halogen, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy or C_{1-4} haloalkoxy;

R^2, R^3 and R^4 are, independently, hydrogen, halogen, cyano, nitro, hydroxy, NR^6R^7, C_{1-6} alkyl (optionally substituted with halogen), C_{1-6} alkoxy (optionally substituted with halogen), $S(O)_p(C_{1-6}$ alkyl), $S(O)_qCF_3$ or $S(O)_2NR^8R^9$;

R^5 is hydrogen, C_{1-6} alkyl or benzyl;

p and q are, independently, 0, 1 or 2;

R^6, R^7, R^8 and R^9 are, independently, hydrogen, C_{1-6} alkyl (optionally substituted by halogen, hydroxy or C_{3-6} cycloalkyl), $CH_2(C_{2-5}$ alkenyl), phenyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^6 and R^7 below), $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^6 and R^7 below), cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^6 and R^7 below), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3) or heterocyclyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^6 and R^7 below), $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^6 and R^7 below), cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^6 and R^7 below), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3);

alternatively NR^6R^7 or NR^8R^9 may, independently, form a 4-7 membered heterocyclic ring, azetidine, pyrrolidine, piperidine, azepine, morpholine or piperazine, the latter optionally substituted by C_{1-4} alkyl on the distal nitrogen;

R^{10}, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} are, independently, hydrogen or C_{1-4} alkyl; or R^{10} and R^{11}, and the carbon to which they are both attached, together form a C_{3-6} cycloalkyl ring, for C_{4-6} cycloalkyl rings said ring optionally having a ring carbon, but not the ring carbon to which R^{10} and R^{11} are both attached, replaced by O, S(O) or $S(O)_2$;

or an N-oxide thereof; or a pharmaceutically acceptable salt thereof.

Certain compounds of the present invention can exist in different isomeric forms (such as enantiomers, diastereomers, geometric isomers or tautomers). The present invention covers all such isomers and mixtures thereof in all proportions.

Suitable salts include acid addition salts such as a hydrochloride, dihydrochloride, hydrobromide, phosphate, sulfate, acetate, diacetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulfonate or *p*-toluenesulfonate. A further example of a suitable salt is benzenesulfonate. In one aspect of the invention A suitable salt is a hydrochloride or an acetate.

The compounds of the invention may exist as solvates (such as hydrates) and the present invention covers all such solvates.

Halogen includes fluorine, chlorine, bromine and iodine. Halogen is, for example, fluorine or chlorine.

Alkyl groups and moieties are straight or branched chain and comprise, for example, 1 to 6 (such as 1 to 4) carbon atoms. Examples of alkyl groups are methyl, ethyl, n-propyl, iso-propyl or tert-butyl.

Haloalkyl groups and moieties comprise an alkyl part, as defined above, and one or more (for example 1 to 6) of the same or different halogen atoms. Haloalkyl is, for example, CH_2F, CHF_2 or CF_3.

Alkenyl groups comprise, for example, 2 to 6 (such as 2 to 4) carbon atoms. Examples of alkenyl groups are vinyl or allyl.

In one embodiment cycloalkyl groups comprise from 3 to 6 carbon atoms and are monocyclic. Cycloalkyl is, for example, cyclopropyl, cyclopentyl or cyclohexyl.

Heterocyclyl is an aromatic or non-aromatic 5 or 6 membered ring, optionally fused to one or more other rings, comprising at least one heteroatom selected from the group comprising nitrogen, oxygen and sulfur; or an N-oxide thereof, or an S-oxide or S-dioxide thereof. Heterocyclyl is, for example, furyl, thienyl (also known as thiophenyl), pyrrolyl, 2,5-dihydropyrrolyl, thiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, piperidinyl, morpholinyl, pyridinyl, dihydropyridinyl (for example in a 6-oxo-1,6-dihydro-pyridinyl moiety), pyrimidinyl, indolyl, 2,3-dihydroindolyl, benzo[b]furyl (also known as benzfuryl), benz[b]thienyl (also known as benzthienyl or benzthiophenyl), 2,3-dihydrobenz[b]thienyl (for example in a 1-dioxo-2,3-dihydrobenz[b]thienyl moiety), indazolyl, benzimidazolyl, benztriazolyl, benzoxazolyl, benzthiazolyl (for example in a 1H-benzthiazol-2-one-yl moiety), 2,3-dihydrobenzthiazolyl (for example in a 2,3-dihydrobenzthiazol-2-one-yl

moiety), 1,2,3-benzothiadiazolyl, an imidazopyridinyl (such as imidazo[1,2-a]pyridinyl), thieno[3,2-b]pyridin-6-yl, 1,2,3-benzoxadiazolyl, benzo[1,2,3]thiadiazolyl, 2,1,3-benzothiadiazolyl, benzofurazan (also known as 2,1,3-benzoxadiazolyl), quinoxalinyl, dihydro-1-benzopyryliumyl (for example in a coumarinyl or a chromonyl moiety), 3,4-dihydro-1H-2,1-benzothiazinyl (for example in a 2-dioxo-3,4-dihydro-1H-2,1-benzothiazinyl moiety), a pyrazolopyridine (for example 1H-pyrazolo[3,4-b]pyridinyl), a purine (for example in a 3,7-dihydro-purin-2,6-dione-8-yl moiety), quinolinyl, isoquinolinyl, dihydroisoquinolinyl (for example in a 2H-isoquinolin-1-one-yl moiety), a naphthyridinyl (for example [1,6]naphthyridinyl or [1,8]naphthyridinyl), a dihydro[1,8]naphthyridinyl (for example in a 1H-[1,8]naphthyridin-4-one-yl moiety), a benzothiazinyl, a dihydrobenzothiazinyl (for example in a 4H-benzo[1,4]thiazin-3-one-yl moiety), benzo[d]imidazo[2,1-b]thiazol-2-yl or dibenzothiophenyl (also known as dibenzothienyl); or an N-oxide thereof, or an S-oxide or S-dioxide thereof.

An N-oxide of a compound of formula (I) is, for example, a 1-oxy-[1,4']bipiperidinyl-1'-yl compound.

In one particular aspect the invention provides a compound of formula (I) wherein W is O.

In another aspect R^1 is phenyl optionally substituted (for example independently mono-, di- or tri-substituted) with halogen (for example chlorine or fluorine), C_{1-4} alkyl (for example methyl or ethyl), cyano or C_{1-4} alkoxy (for example methoxy). In a further aspect R^1 is phenyl optionally substituted (for example independently mono-, di- or tri-substituted) with halogen (for example chlorine or fluorine), C_{1-4} alkyl (for example methyl or ethyl) or cyano.

In yet another aspect R^1 is phenyl optionally substituted (for example independently mono- or di-substituted) with halogen (for example chlorine or fluorine), C_{1-4} alkyl (for example methyl) or C_{1-4} alkoxy (for example methoxy).

In a further aspect R^1 is phenyl optionally substituted (for example with one, two or three of the same or different) with fluorine, chlorine, cyano, C_{1-4} alkyl (for example methyl) or C_{1-4} alkoxy (for example methoxy). In a still further aspect R^1 is phenyl substituted by one, two or three (for example two or three) substituents independently selected from: fluorine, chlorine, cyano and methyl. In another aspect R^1 is 3,4-dichlorophenyl, 2,4-dichloro-3-methylphenyl, 3,4-dichloro-2-methylphenyl, 2,4-dichlorophenyl, 4-chloro-2-methylphenyl, 2-chloro-4-fluorophenyl, 4-fluorophenyl, 3-

chloro-4-cyanophenyl, 3-chloro-4-cyano-2-methylphenyl or 3,4-dichloro-2-ethylphenyl. For example R^1 is 3,4-dichlorophenyl, 2,4-dichloro-3-methylphenyl, 3,4-dichloro-2-methylphenyl, 2,4-dichlorophenyl, 4-chloro-2-methylphenyl, 2-chloro-4-fluorophenyl, 4-fluorophenyl or 3-chloro-4-cyanophenyl. In yet another aspect R^1 is 3,4-dichlorophenyl, 2,4-dichloro-3-methylphenyl, 3,4-dichloro-2-methylphenyl, 3-chloro-4-cyano-2-methylphenyl or 3,4-dichloro-2-ethylphenyl.

In a still further aspect of the invention Q is hydrogen.

In another aspect of the invention R^5 is hydrogen or C_{1-6} alkyl (such as methyl or *tert*-butyl). In a further aspect of the invention R^5 is hydrogen.

In yet another aspect of the present invention R^{10}, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} are, independently, H or C_{1-4} alkyl (for example methyl).

In another aspect of the invention X is oxygen or a bond; and Y is $CR^{10}R^{11}$ or $CR^{10}R^{11}CR^{12}R^{13}$.

In yet another aspect of the invention one of A, B, D, E and G is $CXYCO_2R^5$ and the others are all CH.

In a further aspect of the invention XY is CH_2, CH_2CH_2, OCH_2, $OC(CH_3)_2$ or $OCHCH_3$.

In a still further aspect of the invention when XY is $CR^{10}R^{11}$, $CR^{10}R^{11}CR^{12}R^{13}$ or $CR^{10}R^{11}CR^{12}R^{13}CR^{14}R^{15}$ then A, B or D is $CXYCO_2R^5$.

In another aspect of the invention when XY is $OCR^{10}R^{11}$, $OCR^{10}R^{11}CR^{12}R^{13}$ or $OCR^{10}R^{11}CR^{12}R^{13}CR^{14}R^{15}$ then A, B or D is $CXYCO_2R^5$.

In yet another aspect of the invention R^2, R^3 and R^4, are, independently, hydrogen, halogen, cyano, C_{1-4} alkyl (such as methyl or ethyl), C_{1-4} alkoxy (such as methoxy or ethoxy), CF_3, OCF_3, $S(O)_2(C_{1-4}$ alkyl) (such as $S(O)_2CH_3$) or $S(O)_2NH_2$ {for example R^2, R^3 and R^4, are, independently, hydrogen, halogen, cyano, nitro, C_{1-4} alkyl (such as methyl or ethyl), C_{1-4} alkoxy (such as methoxy or ethoxy), CF_3 or OCF_3}.

In a further aspect of the invention one of R^2, R^3 and R^4 is hydrogen or C_{1-4} alkoxy (such as methoxy).

In a still further aspect the present invention provides a compound of formula (I) wherein: Q is hydrogen; W is O; one of A, B, D, E and G is $CXYCO_2R^5$, another three are CH and one is CR^2; R^1 is phenyl substituted by halogen, cyano or C_{1-4} alkyl (for example optionally substituted by chlorine, cyano, methyl or ethyl); R^2 is hydrogen, halogen (for

example chloro) or C_{1-4} alkoxy (such as methoxy)); R^5 is hydrogen or C_{1-4} alkyl (such as methyl or *tert*-butyl); and XY is CH_2, CH_2CH_2, OCH_2, $OC(CH_3)_2$ or $OCHCH_3$.

In another aspect the present invention provides a compound of formula (I) wherein: Q is hydrogen; W is O; E is CH; one of A, B, D and G is $CXYCO_2H$, and the others are CR^2, CR^3 and CR^4 (wherein R^2, R^3 and R^4 are, independently, hydrogen or C_{1-4} alkoxy (such as methoxy)); R^1 is phenyl substituted by halogen (for example by one or two chlorine atoms); and XY is CH_2, CH_2CH_2, OCH_2, $OC(CH_3)_2$ or $OCHCH_3$.

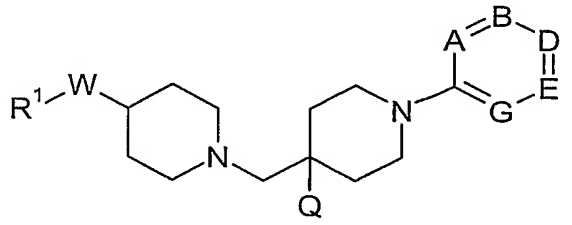
The compounds of the present invention can be prepared as described below.

A compound of formula (I) wherein R^5 is H can be prepared from a compound of formula (I) wherein R^5 is alkyl by hydrolysis, for example with a suitable hydroxide (such as an alkali metal hydroxide, for example lithium hydroxide) in a suitable solvent (for example a C_{1-6} aliphatic alcohol such as methanol) typically at room temperature (for example 10-30°C).

A compound of formula (I) wherein R^5 is H can be prepared from a compound of formula (I) wherein R^5 is alkyl by hydrolysis, for example with an acid (such as an hydrochloric acid or trifluoroacetic acid) in a suitable solvent (for example water or dichloromethane) typically at room temperature to reflux (for example 10-100 °C).

A compound of formula (I) where R^5 is alkyl can be formed from a compound of formula (I) where R^5 is H by procedures (such as esterification) which are well-known in the art.

A compound of formula (I) wherein R^5 is H can be formed from a compound of formula (II):

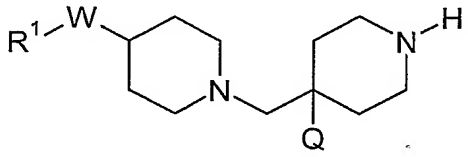


(II)

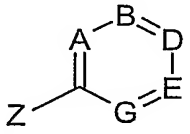
wherein one of A, B, D, E, or G represents CXYCN by hydrolysis of the nitrile under conditions well-known in the art.

A compound of formula (I) or (II) can be prepared by reacting a compound of formula (III) with a compound of formula (IV) (wherein A, B, D, E, G are as defined above for formula (I) or (II), and Z is Br, I) in the presence of copper iodide, proline and a

base (such as potassium carbonate) in a suitable solvent (for example DMSO) at a suitably elevated temperature (such as 60-100°C, such as at around 80°C).



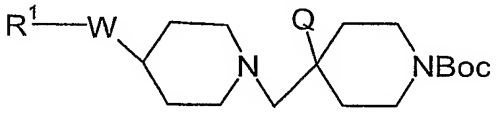
(III)



(IV)

Alternatively a compound of formula (I) can be prepared by reacting a compound of formula (III) with a compound of formula (IV) (wherein A, B, D, E, G as defined above for formulae (I) or (II), and Z is Br, I) in the presence of a palladium salt (such as palladium acetate), a phosphine (such as BINAP or dicyclohexyl-(2',4',6'-triisopropyl-biphenyl-2-yl)-phosphane) and a base (for example caesium carbonate), in a suitable solvent (for example toluene) at a suitably elevated temperature (for example 80 – 100°C).

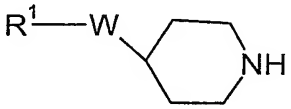
A compound of formula (III) can be prepared by deprotecting a compound of formula (V):



(V)

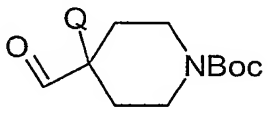
for example using trifluoroacetic acid in a suitable solvent (such as dichloromethane); or using a source of hydrogen chloride in a suitable solvent (such as dioxane).

A compound of formula (V), wherein Q is hydrogen, can be prepared by reacting a compound of formula (VI):



(VI)

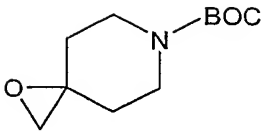
with a compound of formula (VII):



(VII)

in the presence of $NaBH(OAc)_3$ and acetic acid, in a suitable solvent (such as tetrahydrofuran or dichloromethane).

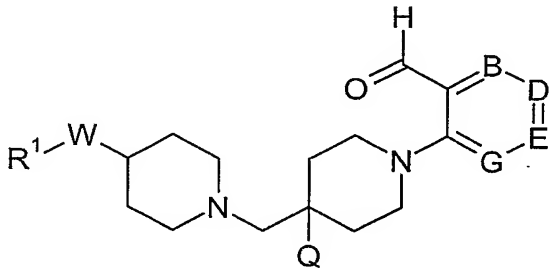
A compound of formula (V), wherein Q is hydroxy, can be prepared by reacting a compound of formula (VI) with a compound of formula (VIII):



(VIII)

in a suitable solvent (such as a C_{1-6} aliphatic alcohol, for example ethanol) at room temperature.

A compound of formula (I) wherein A is $CXYCO_2R^5$ can be prepared by reacting a compound of formula (IX):

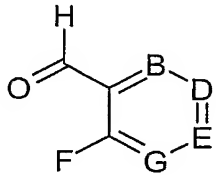


(IX)

with methyl methylthiomethyl sulfoxide or ethyl ethylthiomethyl sulfoxide in the presence of a base (such as sodium hydride), in a suitable solvent (for example THF), at a suitable temperature (such as in the range 10 to -20°C, for example 0°C), and treating the product resulting therefrom with HCl in R^5OH.

A compound of formula (II), wherein A is CXYCN, can be prepared by reacting a compound of formula (IX) with toluenesulfonylmethyl isocyanide in the presence of a base (such as potassium *tert*-butoxide), in a suitable solvent (for example dimethoxyethane) at a temperature between –78°C and 0°C.

A compound of formula (IX) can be prepared by reacting a compound of formula (III) with a compound of formula (X):

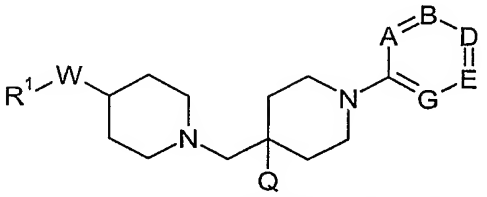


(X)

in the presence of a base (for example potassium carbonate), in a suitable solvent (for example dimethylacetamide) at a temperature of 80 – 100°C.

A compound of formula (I) wherein XY is $OCR^{10}R^{11}$, $OCR^{10}R^{11}CR^{12}R^{13}$ or $OCR^{10}R^{11}CR^{12}R^{13}CR^{14}R^{15}$ can be prepared by reacting a compound of formula (XI), wherein one of A, B, D, E, or G represents COH, with a compound of formula (XII), wherein L is halogen or a sulfonate ester (for example tosylate), and n and m are,

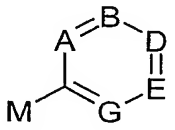
independently, 0 or 1, in the presence of a base (for example potassium carbonate), in a suitable solvent (for example DMF) at ambient temperature (for example 10-30°C).



(XI)

$LC(R^{10}R^{11})[C(R^{12}R^{13})]_n[C(R^{14}R^{15})]_mCOOR^5$ (XII)

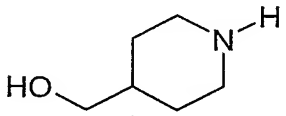
A compound of formula (XI) can be prepared by reacting a compound of formula (III) with a compound of formula (XIII)



(XIII)

wherein M is bromine or iodine and one of A, B, D, E, or G is COH, in the presence of copper iodide, proline and a base (for example potassium carbonate) in a suitable solvent (for example DMSO) at a suitable elevated temperature (such as in the range 60-100°C, for example around 80°C. (Note that in one embodiment of the process of the invention the phenol is protected as an ether (such as a methyl ether) using methods of protection and deprotection described below).

Alternatively any procedure using a compound of formula (III) can be carried out under similar conditions with a compound of formula (XIV):

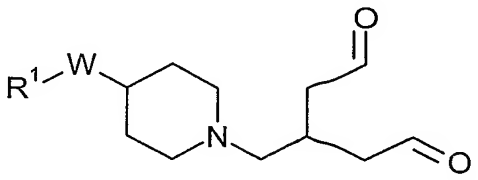


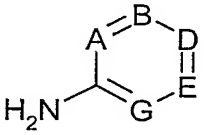
(XIV)

(wherein the hydroxy group is, for example, protected). The resultant product can then be oxidised to an aldehyde (for example under Swern conditions), and then condensed with a compound of formula (VI) in the presence of $NaBH(OAc)_3$ and acetic acid, in a suitable solvent (such as tetrahydrofuran or dichloromethane) to give a compound of formula (I), (II), or (XI). Alternatively these steps can be conducted in a different order; for example it is possible to proceed via a compound of formula (IX) providing that reaction of the aromatic aldehyde occurred before the Swern oxidation to produce the aldehyde that is reductively aminated.

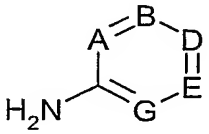
Alternatively a compound of formula (I) where Q represents H may be prepared by reaction of a compound of formula (XV) with a compound of formula (XVI) (wherein A, B, D, E, G are as defined above for formula (I) or (II)) in the presence of a suitable

reducing agent, for example sodium tricetoxyborohydride or sodium cyanoborohydride, and acetic acid, in a suitable solvent (such as tetrahydrofuran or dichloromethane).

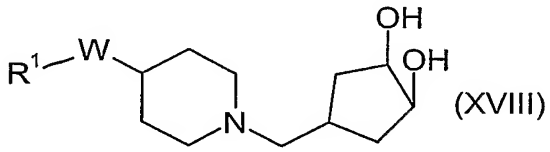

(XV)


(XVI)

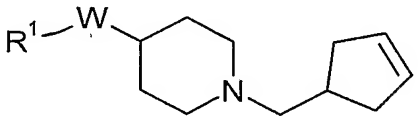
Similarly a compound of formula (XI) may be prepared by reacting a compound of formula (XV) with a compound of formula (XVII) wherein A, B, D, E, and G are defined as in formula (XIII).


(XVII)

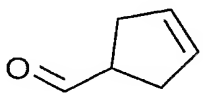
A compound of formula (XV) can be prepared by reacting a compound of formula (XVIII):with lead tetra-acetate in the presence of sodium carbonate in dichloromethane or with sodium periodate in water.


(XVIII)

A compound of formula (XVIII) may be prepared by oxidising a compound of formula (XIX) with osmium tetroxide in the presence of N-methyl morpholine N-Oxide (NMMO) in aqueous acetone at ambient (say 10-30°C) temperature. Alternatively a compound of formula (XVIII) may be prepared as described in WO2004029041.


(XIX)

A compound of formula (XIX) may be prepared by reaction of a compound of fomula (VI) with a compound fo formula (XX) in the presence of a suitable reducing agent, for example sodium tricetoxyborohydride or sodium cyanoborohydride, and acetic acid, in a suitable solvent (such as tetrahydrofuran or dichloromethane).


(XX)

The preparation of various intermediates can be found in WO00/66559 and WO01/77101; alternatively they can be prepared by using or adapting literature methods.

Further compounds of formula (I) can be prepared by adaptation of: the routes described above, methods described in the art or the Examples recited below.

Compounds of formula (III) to (XX) can be prepared by using or adapting methods described in the art. The preparation of various phenoxy piperidines is described in WO 01/77101.

In the above processes it may be desirable or necessary to protect an acid group or a hydroxy or other potentially reactive group. Suitable protecting groups and details of processes for adding and removing such groups may be found in "Protective Groups in Organic Synthesis", 3rd Edition (1999) by Greene and Wuts.

In another aspect the present invention provides processes for the preparation of compounds of formula (I).

The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of chemokine receptor (such as CCR3) activity, and may be used in the treatment of autoimmune, inflammatory, proliferative or hyperproliferative diseases, or immunologically-mediated diseases (including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS)).

Examples of these conditions are:

(1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; bronchitis {such as eosinophilic bronchitis}; acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung, idiopathic interstitial pneumonia, antitussive activity, treatment of chronic cough associated with inflammatory conditions of the airways or iatrogenic induced cough;

(2) (bone and joints) arthritides including rheumatic, infectious, autoimmune, seronegative spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis or Reiter's disease), Behçet's disease, Sjogren's syndrome or systemic sclerosis;

(3) (pain and connective tissue remodelling of musculoskeletal disorders due to injury [for example sports injury] or disease) arthitides (for example rheumatoid arthritis, osteoarthritis, gout or crystal arthropathy), other joint disease (such as intervertebral disc degeneration or temporomandibular joint degeneration), bone remodelling disease (such as osteoporosis, Paget's disease or osteonecrosis), polychondritits, scleroderma, mixed connective tissue disorder, spondyloarthropathies or periodontal disease (such as periodontitis);

(4) (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczmatous dermitides, seborrhoetic dermatitis, lichen planus, phemphigus, bullous phemphigus, epidermolysis bullosa, urticaria, angiodermas, vasculitides erythemas, cutaneous eosinophilias, uveitis, alopecia areata, corneal ulcer or vernal conjunctivitis;

(5) (gastrointestinal tract) Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease or food-related allergies which have effects remote from the gut (for example migraine, rhinitis or eczema);

(6) (Allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea; or chronic graft versus host disease; and/or

(7) (other tissues or diseases) Alzheimer's disease, multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus disorders (such as lupus erythematosus or systemic lupus), erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, leprosy (such as lepromatous leprosy), peridontal disease, Sezary syndrome, idiopathic thrombocytopenia pupura or disorders of the menstrual cycle.

The compounds of formula (I) or a pharmaceutically acceptable salt thereof, are also H1 antagonists (and can, therefore, be used in the treatment of allergic disorders); and may also be used to control a sign and/or symptom of what is commonly referred to as a cold (for example a sign and/or symptom of a common cold or influenza or other associated respiratory virus infection).

According to a further feature of the present invention there is provided a method for treating a chemokine mediated disease state (such as a CCR3 mediated disease state) in a mammal, such as man, suffering from, or at risk of, said disease state, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof.

According to another feature of the present invention there is provided a method for antagonising H1 in a mammal, such as man, suffering from, or at risk of, an H1 mediated disease state, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof.

According to yet another feature of the present invention there is provided a method for treating a sign and/or symptom of what is commonly referred to as a cold in a mammal, such as man, suffering from, or at risk of, said disease state, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof.

The invention also provides a compound of the formula (I), or a pharmaceutically acceptable salt thereof, for use in therapy.

In another aspect the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in therapy (for example modulating chemokine receptor activity (such as CCR3 receptor activity), antagonising H1 or treating a sign and/or symptom of what is commonly referred to as a cold).

The invention further provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of:

(1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; bronchitis {such as eosinophilic bronchitis}; acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofulous rhinitis; seasonal rhinitis including rhinitis

nervosa (hay fever) or vasomotor rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung, idiopathic interstitial pneumonia, antitussive activity, treatment of chronic cough associated with inflammatory conditions of the airways or iatrogenic induced cough;

(2) (bone and joints) arthritides including rheumatic, infectious, autoimmune, seronegative spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis or Reiter's disease), Behçet's disease, Sjogren's syndrome or systemic sclerosis;

(3) (pain and connective tissue remodelling of musculoskeletal disorders due to injury [for example sports injury] or disease) arthitides (for example rheumatoid arthritis, osteoarthritis, gout or crystal arthropathy), other joint disease (such as intervertebral disc degeneration or temporomandibular joint degeneration), bone remodelling disease (such as osteoporosis, Paget's disease or osteonecrosis), polychondritits, scleroderma, mixed connective tissue disorder, spondyloarthropathies or periodontal disease (such as periodontitis);

(4) (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczmatous dermitides, seborrhoetic dermatitis, lichen planus, phemphigus, bullous phemphigus, epidermolysis bullosa, urticaria, angiodermas, vasculitides erythemas, cutaneous eosinophilias, uveitis, alopecia areata, corneal ulcer or vernal conjunctivitis;

(5) (gastrointestinal tract) Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease or food-related allergies which have effects remote from the gut (for example migraine, rhinitis or eczema);

(6) (Allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea; or chronic graft versus host disease; and/or

(7) (other tissues or diseases) Alzheimer's disease, multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus disorders (such as lupus erythematosus or systemic lupus), erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, leprosy (such as lepromatous leprosy), Peridontal disease, sezary syndrome, idiopathic thrombocytopenia pupura or disorders of the menstrual cycle;

in a mammal (for example man).

In a further aspect the invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; or rhinitis {including acute, allergic, atrophic or chronic rhinitis, such as rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis}.

In a still further aspect a compound of formula (I), or a pharmaceutically acceptable salt thereof, is useful in the treatment of asthma.

The present invention also provides a the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; or rhinitis {including acute, allergic, atrophic or chronic rhinitis, such as rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis}.

In order to use a compound of the invention, or a pharmaceutically acceptable salt thereof, for the therapeutic treatment of a mammal, such as man, said ingredient is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition. Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt thereof (active ingredient), and a pharmaceutically acceptable adjuvant, diluent or carrier.

In a further aspect the present invention provides a process for the preparation of said composition which comprises mixing active ingredient with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will, for example, comprise from 0.05 to 99 %w (per cent by weight), such as from 0.05 to 80 %w, for example from 0.10 to 70 %w, such as from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by topical (such as to the lung and/or airways or to the skin), oral, rectal or parenteral administration. For these purposes the compounds of this invention may be formulated by means known in the art. A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 0.1mg and 1g of active ingredient.

Each patient may receive, for example, a dose of $0.01mgkg^{-1}$ to $100mgkg^{-1}$, such as in the range of $0.1mgkg^{-1}$ to $20mgkg^{-1}$, of the active ingredient administered, for example, 1 to 4 times per day.

The invention further relates to combination therapies wherein a compound of formula (1) or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, or a pharmaceutical composition or formulation comprising a compound of formula (1) is administered concurrently or sequentially or as a combined preparation with another therapeutic agent or agents, for the treatment of one or more of the conditions listed.

In particular, for the treatment of the inflammatory diseases such as (but not restricted to) rheumatoid arthritis, osteoarthritis, asthma, allergic rhinitis, chronic obstructive pulmonary disease (COPD), psoriasis, and inflammatory bowel disease, the compounds of the invention may be combined with agents such as:- Non-steroidal anti-inflammatory agents (hereinafter NSAIDs) including non-selective cyclo-oxygenase COX-1 / COX-2 inhibitors whether applied topically or systemically (such as piroxicam, diclofenac, propionic acids such as naproxen, flurbiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, azapropazone, pyrazolones such as phenylbutazone, salicylates such as aspirin); selective COX-2 inhibitors (such as meloxicam, celecoxib, rofecoxib, valdecoxib, lumarocoxib, parecoxib and etoricoxib); cyclo-oxygenase inhibiting nitric oxide donors (CINODs); glucocorticosteroids (whether administered by topical, oral, intramuscular, intravenous, or intra-articular routes); methotrexate, leflunomide; hydroxychloroquine, d-penicillamine, auranofin or other parenteral or oral gold preparations ; analgesics; diacerein; intra-articular therapies such as hyaluronic acid derivatives; and nutritional supplements such as glucosamine.

The present invention still further relates to the combination of a compound of the invention together with a cytokine or agonist or antagonist of cytokine function, (including agents which act on cytokine signalling pathways such as modulators of the SOCS system) including alpha-, beta-, and gamma-interferons; insulin-like growth factor type I (IGF-1); interleukins (IL) including IL1 to 17, and interleukin antagonists or inhibitors such as anakinra; tumour necrosis factor alpha (TNF-α) inhibitors such as anti-TNF monoclonal antibodies (for example infliximab; adalimumab , and CDP-870) and TNF receptor antagonists including immunoglobulin molecules (such as etanercept) and low-molecular-weight agents such as pentoxyfylline.

The present invention still further relates to the combination of a compound of the invention together with modulators of chemokine receptor function such as antagonists of CCR1, CCR2, CCR2A, CCR2B, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX_3CR1 for the C-X_3-C family.

The present invention still further relates to the combination of a compound of the invention together with an inhibitor of matrix metalloproteases (MMPs), i.e., the stromelysins, the collagenases, and the gelatinases, as well as aggrecanase; such as collagenase-1 (MMP-1), collagenase-2 (MMP-8), collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), and stromelysin-3 (MMP-11) and MMP-9 and MMP-12, including agents such as doxycycline.

The present invention still further relates to the combination of a compound of the invention together with a leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist such as; zileuton; ABT-761; fenleuton; tepoxalin; Abbott-79175; Abbott-85761; N-(5-substituted)-thiophene-2-alkylsulfonamides; 2,6-di-tert-butylphenolhydrazones; methoxytetrahydropyrans such as Zeneca ZD-2138; the compound SB-210661; pyridinyl-substituted 2-cyanonaphthalene compounds such as L-739,010; 2-cyanoquinoline compounds such as L-746,530; indole and quinoline compounds such as MK-591, MK-886, and BAY x 1005.

The present invention still further relates to the combination of a compound of the invention together with a receptor antagonist for leukotrienes (LT) B4, LTC4, LTD4, and LTE4 selected from the group consisting of the phenothiazin-3-1s such as L-651,392; amidino compounds such as CGS-25019c; benzoxalamines such as ontazolast; benzenecarboximidamides such as BIIL 284/260; and compounds such as zafirlukast,

ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195.

The present invention still further relates to the combination of a compound of the invention together with a phosphodiesterase (PDE) inhibitor such as the methylxanthanines including theophylline and aminophylline; and selective PDE isoenzyme inhibitors including PDE4 inhibitors and inhibitors of the isoform PDE4D, and inhibitors of PDE5.

The present invention still further relates to the combination of a compound of the invention together with histamine type 1 receptor antagonists such as cetirizine, loratadine, desloratadine, fexofenadine, acrivastine, terfenadine, astemizole, azelastine, levocabastine, chlorpheniramine, promethazine, cyclizine, and mizolastine applied orally, topically or parenterally.

The present invention still further relates to the combination of a compound of the invention together with a proton pump inhibitor (such as omeprazole) or gastroprotective histamine type 2 receptor antagonist.

The present invention still further relates to the combination of a compound of the invention with antagonists of the histamine type 4 receptor.

The present invention still further relates to the combination of a compound of the invention together with an alpha-1/alpha-2 adrenoceptor agonist vasoconstrictor sympathomimetic agent, such as propylhexedrine, phenylephrine, phenylpropanolamine, ephedrine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, tramazoline hydrochloride, and ethylnorepinephrine hydrochloride.

The present invention still further relates to the combination of a compound of the invention together with anticholinergic agents including muscarinic receptor (M1, M2, and M3) antagonists such as atropine, hyoscine, glycopyrrrolate, ipratropium bromide, tiotropium bromide, oxitropium bromide, pirenzepine, and telenzepine.

The present invention still further relates to the combination of a compound of the invention together with a beta-adrenoceptor agonist (including beta receptor subtypes 1-4) such as isoprenaline, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, and pirbuterol, including chiral enantiomers thereof.

The present invention still further relates to the combination of a compound of the invention together with a chromone, including sodium cromoglycate and nedocromil sodium.

The present invention still further relates to the combination of a compound of the invention together with a glucocorticoid, such as flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, ciclesonide, and mometasone furoate.

The present invention still further relates to the combination of a compound of the invention together with an agent that modulate nuclear hormone receptors such as PPARs.

The present invention still further relates to the combination of a compound of the invention together with an immunoglobulin (Ig) or Ig preparation or an antagonist or antibody modulating Ig function such as anti-IgE (e.g. omalizumab).

The present invention still further relates to the combination of a compound of the invention together with other systemic or topically-applied anti-inflammatory agents including thalidomide and derivatives, retinoids, dithranol, and calcipotriol.

The present invention still further relates to the combination of a compound of the invention together with combinations of aminosalicylates and sulfapyridine such as sulfasalazine, mesalazine, balsalazide, and olsalazine; and immunomodulatory agents such as the thiopurines, and corticosteroids such as budesonide.

The present invention still further relates to the combination of a compound of the invention together with an antibacterial agent including penicillin derivatives, tetracyclines, macrolides, beta-lactams, fluoroquinolones, metronidazole, and inhaled aminoglycosides; and antiviral agents including acyclovir, famciclovir, valaciclovir, ganciclovir, cidofovir; amantadine, rimantadine; ribavirin; zanamavir and oseltamavir; protease inhibitors such as indinavir, nelfinavir, ritonavir, and saquinavir; nucleoside reverse transcriptase inhibitors such as didanosine, lamivudine, stavudine, zalcitabine, zidovudine; non-nucleoside reverse transcriptase inhibitors such as nevirapine, efavirenz.

The present invention still further relates to the combination of a compound of the invention together with cardiovascular agents such as calcium channel blockers, beta-adrenoceptor blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-2 receptor antagonists; lipid lowering agents such as statins, and fibrates; modulators of blood cell morphology such as pentoxyfylline; thrombolytics, and anticoagulants including platelet aggregation inhibitors.

The present invention still further relates to the combination of a compound of the invention together with CNS agents such as antidepressants (such as sertraline), anti-Parkinsonian drugs (such as deprenyl, L-dopa, ropinirole, pramipexole, MAOB inhibitors

such as selegine and rasagiline, comP inhibitors such as tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, nicotine agonists, dopamine agonists and inhibitors of neuronal nitric oxide synthase), and anti-Alzheimer's drugs such as donepezil, rivastigmine, tacrine, COX-2 inhibitors, propentofylline or metrifonate.

The present invention still further relates to the combination of a compound of the invention together with agents for the treatment of acute and chronic pain, including centrally and peripherally-acting analgesics such as opioid analogues and derivatives, carbamazepine, phenytoin, sodium valproate, amitryptiline and other antidepressant agents, paracetamol, and non-steroidal anti-inflammatory agents.

The present invention still further relates to the combination of a compound of the invention together with parenterally or topically-applied (including inhaled) local anaesthetic agents such as lignocaine and analogues.

The compounds of the present invention may also be used in combination with anti-osteoporosis agents including hormonal agents such as raloxifene, and biphosphonates such as alendronate.

The present invention still further relates to the combination of a compound of the invention together with (i) tryptase inhibitors; (ii) platelet activating factor (PAF) antagonists; (iii) interleukin converting enzyme (ICE) inhibitors; (iv) IMPDH inhibitors; (v) adhesion molecule inhibitors including VLA-4 antagonists; (vi) cathepsins; (vii) Kinase inhibitors including but not limited to inhibitors of tyrosine kinases (such as Btk, Itk, Jak3 MAP examples of inhibitors might include Gefitinib, Imatinib mesylate), Serine / threonine kinases (including but not limited to inhibitors of MAP kinases such as p38, JNK, protein kinases A, B and C and IKK), and kinases involved in cell cycle regulation (such as but not limted to the cylin dependent kinases); (viii) glucose-6 phosphate dehydrogenase inhibitors; (ix) kinin-B_1 - and B_2 -receptor antagonists; (x) anti-gout agents, e.g., colchicine; (xi) xanthine oxidase inhibitors, e.g., allopurinol; (xii) uricosuric agents, e.g., probenecid, sulfinpyrazone, and benzbromarone; (xiii) growth hormone secretagogues; (xiv) transforming growth factor (TGFβ); (xv) platelet-derived growth factor (PDGF); (xvi) fibroblast growth factor, e.g., basic fibroblast growth factor (bFGF); (xvii) granulocyte macrophage colony stimulating factor (GM-CSF); (xviii) capsaicin cream; (xix) tachykinin NK_1 and NK_3 receptor antagonists such as the group consisting of NKP-608C; SB-233412 (talnetant); and D-4418; (xx) elastase inhibitors such as the group consisting of UT-77 and ZD-0892; (xxi) TNF-alpha converting enzyme inhibitors (TACE);

(xxii) induced nitric oxide synthase (iNOS) inhibitors or (xxiii) chemoattractant receptor-homologous molecule expressed on TH2 cells, (such as CRTH2 antagonists) (xxiv) inhibitors of P38 (xxv) agents modulating the function of Toll-like receptors (TLR) and (xxvi) agents modulating the activity of purinergic receptors such as P2X7; (xxvii) inhibitors of transcription factors activation such as NFkB, API, and STATS.

The compounds of the invention can also be used in combination with existing therapeutic agents for the treatment of cancer. Suitable agents to be used in combination include:

(i) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine and paclitaxel; antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecins);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and iodoxyfene), oestrogen receptor down regulators (for example fulvestrant), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5α-reductase such as finasteride;

(iii) Agents which inhibit cancer cell invasion (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);

(iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies (for example the anti-erbb2 antibody trastuzumab and the anti-erbb1 antibody cetuximab [C225]) , farnesyl transferase inhibitors, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase

inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab, compounds such as those disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354) and compounds that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function and angiostatin);

(vi) vascular damaging agents such as combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213;

(vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

(ix) immunotherapeutic approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) when given, ^{1}H NMR data is quoted and is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300MHz or 400MHz using perdeuterio DMSO-D6

(CD_3SOCD_3) or $CDCl_3$ as the solvent unless otherwise stated;

(ii) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (CI) mode using a direct exposure probe; where indicated ionisation was effected by electron impact (EI) or fast atom bombardment (FAB); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$;

(iii) the title and sub-title compounds of the examples and methods were named using the ACD/name program from Advanced Chemistry Development Inc, version 6.00;

(iv) unless stated otherwise, reverse phase HPLC was conducted using a Symmetry™, NovaPak™ or Xerra™ reverse phase silica column;

(v) for analytical HPLC the following conditions were used:

Reverse phase analytical HPLC (Hewlett Packard Series 1100) using Waters "Symmetry" C8 column 3.5μm; 4.6 x 50mm column using 0.1% ammonium acetate/acetonitrile gradients at 2 mL/min given as % aqueous

Standard 75% to 5% over 3 min

Fast 45% to 5% over 2.5 min

Medium fast 65% to 5% in 2.5 min

Slow 95% to 50% in 2.5 min

Superslow 100% to 80% in 2.5 min;

Other gradients are reported as aqueous/starting % aq/final % aq/organic/time (in minutes) where NH4 represents 0.1% ammonium acetate and A represents acetonitrile;

and

(vi) the following abbreviations are used:

RPHPLC	Reverse phase HPLC	DMSO	dimethylsulfoxide
HPLC	high pressure liquid chromatography	aq	aqueous
TFA	Trifluoroacetic acid	RT	room temperature
DMF	N,N-dimethylformamide	TBME	tert-butyl methyl ether
Ret	Retention time		

Intermediate 1

This illustrates the preparation of 4-(3,4-dichloro-2-ethylphenoxy)piperidine

a) 1,2-dichloro-3-ethyl-4-fluorobenzene

1,2-Dichloro-4-fluorobenzene (1.3 mL) was dissolved in THF (10 mL) and the resultant solution was cooled to –78 °C. *n*-Butyl lithium (10M, 1.2 mL) was added dropwise over 5 min. The resultant solution was stirred at –78 °C for 5 min then allowed to warm to ca -40 °C and held at this temperature for 15 min. The solution was cooled to -78 °C and then iodoethane (1.24 mL) was added. The resultant solution was allowed to warm to 10 °C. pH7 Buffer was added followed by ethyl acetate and diethyl ether. The phases were separated and the aqueous phase was extracted twice with diethyl ether. The organics were combined, washed with brine, dried, filtered and concentrated to give the title compound, contaminated with diethyl ether and ethyl acetate. (2.37 g).

GCMS 97.75% retention time 4.61 min (M^+ (EI) 192/194/196; bp 177) (Agilent 6890/5973 GC/MSD HP5-MS column, 30m x 0.25mm with a film thickness of 0.25um, 90-310 °C at 30 °C/min).

^{1}H NMR $\delta_{(CDCl3)}$ 1.18 (3H, t), 2.84 (2H, qd), 6.92 (1H, t), 7.27 (1H, dd).

b) 4-(3,4-Dichloro-2-ethylphenoxy)piperidine

1,2-Dichloro-3-ethyl-4-fluoro-benzene (2.37 g), 4-hydroxypiperidine (1.24 g) and potassium t-butoxide (1.47 g) were charged to a flask. 1-methyl-2-pyrrolidinone (12 mL) was added and the mixture was stirred and heated to 65 °C for 6 h.

2M HCl aq was added and the mixture was extracted twice with ethyl acetate. The aqueous phase was neutralised with aqueous with sodium carbonate and extracted thrice with ethyl acetate, dried, filtered and concentrated.

The residue was dissolved in ether and washed with sodium hydroxide solution (2M), water (thrice) and brine. The organic phase was dried, filtered and evaporated to give the title compound (1.22 g) as a yellow oil.

LCMS (standard gradient) RT 1.91 (ES+ 274/276/278).

^{1}H NMR $\delta_{(CDCL3)}$ 1.10 (3H, t), 2.01 - 2.10 (2H, m), 2.20 - 2.29 (2H, m), 2.39 (3H, s), 2.81 (2H, q), 3.28 - 3.38 (4H, m), 4.53 - 4.58 (1H, m), 6.62 (1H, d), 7.20 - 7.25 (3H, m), 7.77 (2H, d), 8.84 - 8.95 (1H, m), 9.01 - 9.12 (1H, m).

Intermediate 2

This illustrates the preparation of 4-(3,4-dichlorophenoxy)-1-(4-piperidinylmethyl)-piperidine

a) 1,1-Dimethylethyl 4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-1-piperidinecarboxylate

4-(3,4-Dichlorophenoxy)piperidine (1.27 g) was dissolved in tetrahydrofuran (20 mL); acetic acid (0.5 mL) and *tert*-butyl 4-formylpiperidine-1-carboxylate (1.43 g) were added to the solution. The reaction mixture was stirred at room temperature for 30 min then sodium triacetoxyborohydride (1.53 g) was added and the mixture was stirred at room temperature overnight. The reaction mixture was poured into 2M sodium hydroxide solution (50 mL) and product was extracted with diethyl ether. The combined ether extracts were washed with brine, dried, filtered and evaporated. Crude material was purified by flash chromatography, (eluting with 979:20:1 dichloromethane : methanol : aqueous ammonia) to give the sub-title compound (2.15 g).

MS 443/445 $[M+H]^+$ (ES+).

^{1}H NMR $\delta_{(CDCl3)}$ 1.06 (2H, ddd), 1.45 (9H, s), 1.61 - 1.82 (5H, m), 1.92 - 1.98 (2H, m), 2.16 - 2.27 (4H, m), 2.65 - 2.73 (4H, m), 4.08 (2H, d), 4.25 (1H, dq), 6.75 (1H, dd), 6.99 (1H, d), 7.30 (1H, d).

b) 4-(3,4-Dichlorophenoxy)-1-(4-piperidinylmethyl)-piperidine

1,1-Dimethylethyl 4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidine-1-carboxylate (1.0 g) was added to a mixture of 20% TFA in dichloromethane (20 mL) and the mixture was stirred at room temperature for 1 h. Solvent was removed by evaporation and 2M sodium hydroxide solution (25 mL) was added to the residue. The product was extracted with ethyl acetate and the organic phase was washed with brine, dried, filtered and evaporated to give the title compound (0.5 g).

MS 343/345 $[M+H]^+$ (ES+).

^{1}H NMR $\delta_{(CDCl3)}$ 1.10 (2H, qd), 1.60 (1H, qquintet), 1.73 - 1.83 (4H, m), 1.90 - 2.01 (2H, m), 2.16 - 2.26 (4H, m), 2.55 - 2.70 (4H, m), 3.09 (2H, d), 4.24 (1H, dquintet), 6.75 (1H, dd), 6.99 (1H, d), 7.27 (1H, d).

The following Intermediates were prepared analogously from the appropriate aryloxy piperidine:

Intermediate	Name (M+H)	^{1}H NMR $\delta_{(CDCl3)}$
3	4-(2,4-Dichloro-3-methylphenoxy)-1-(4-piperidinylmethyl)-piperidine (357/359)	1.13 - 1.27 (2H, m), 1.57 - 1.70 (1H, m), 1.76 - 2.00 (2H, m), 2.16 - 2.32 (4H, m), 2.46 (3H, s), 2.60 - 2.99 (8H, m), 3.16 (2H, d), 4.31 (1H, quintet), 6.75 (1H, d), 7.18 (1H, d)
4	4-(4-Chloro-2-methylphenoxy)-1-(4-piperidinylmethyl)-piperidine (322/324)	1.08 - 1.21 (2H, m), 1.56 - 1.68 (1H, m), 1.73 - 1.86 (4H, m), 1.90 - 1.99 (2H, m), 2.16 - 2.31 (7H, m), 2.57 - 2.69 (4H, m), 3.12 (2H, d), 4.23 - 4.31 (1H, m), 6.74 (1H, d), 7.06 (1H, dd), 7.11 (1H, d)

Intermediate 5

This illustrates the preparation of 2-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenol

4-(3,4-Dichlorophenoxy)-1-{[1-(2-methoxyphenyl)piperidin-4-yl]methyl}piperidine

4-(3,4-Dichlorophenoxy)-1-(piperidin-4-ylmethyl)piperidine (1.0 g), 1-iodo-2-methoxybenzene (0.68 g), copper iodide (55 mg), L-proline (66 mg) and K_2CO_3 (0.8 g) were suspended in DMSO and heated to 80 °C for 16 h. The mixture was diluted with water and then extracted using EtOAc (3x 100 mL). The organic layers were combined, washed with brine, dried and the solvents were evaporated. The residue was purified by chromatography (EtOAc) to give the subtitle compound (0.20 g).

HPLC Ret. standard. 2.9.

MS (ES+ve) 449/451 $(M+H)^+$

2-(4-{[4-(3,4-Dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenol

4-(3,4-Dichlorophenoxy)-1-{[1-(2-methoxyphenyl)piperidin-4-yl]methyl}piperidine (0.15 g) was dissolved in dichloromethane (2 mL) and the solution was cooled to -30 °C in an ice bath (dry ice/acetonitrile). Tribromoborane (1M solution in dichloromethane, 2.6 mL) was added. The reaction mixture was allowed to warm to 0 °C over 4 h. Methanol (2 mL) was carefully added while the reaction mixture was kept at

0 °C. The solvents were evaporated and the residue was dissolved in MeOH and then purified by RPHPLC (gradient 75% - 5% aqueous ammonium acetate, 25% - 95% acetonitrile) to give the subtitle compound (100 mg).

HPLC Ret. fast 2.02

MS (ES+ve) 435/437 $(M+H)^+$

The following intermediate was prepared analogously to Intermediate 5 using the appropriate iodophenol

Intermediate	Name	MS (ES+ve) $(M+H)^+$	Retention time gradient
6	2-(4-{[4-(3,4-Dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenol	435/437	2.75 std

Intermediate 7

This illustrates the preparation of 2-chloro-4-({1-[(3,4-dihydroxycyclopentyl)-methyl]piperidin-4-yl}oxy)-3-methylbenzonitrile

a) 2-Chloro-4-{[1-(cyclopent-3-en-1-ylmethyl)piperidin-4-yl]oxy}-3-methylbenzonitrile

2-Chloro-3-methyl-4-(piperidin-4-yloxy)benzonitrile (1.3 g) (WO2004099144), acetic acid (0.32 mL), sodium triacetoxyborohydride (1.4 g) and tetrahydrofuran (20 mL) were combined and stirred under nitrogen. Cyclopent-3-ene-1-carbaldehyde (0.5 g) was added and stirring continued for 1h. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between a saturated solution of sodium bicarbonate in water and dichloromethane. The dichloromethane was washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Crude product was purified by flash chromatography to give the subtitle compound as a colourless oil, (1.5 g).

^1H NMR $\delta_{(CDCL3)}$ 1.78 - 1.90 (2H, m), 1.93 - 2.14 (4H, m), 2.28 - 2.39 (7H, m), 2.41 - 2.53 (3H, m), 2.63 - 2.72 (2H, m), 4.38 - 4.48 (1H, m), 5.64 (2H, s), 6.79 (1H, d), 7.46 (1H, d); MS: 331/333 $[M+H]^+$; Retention time: 2.66 min on standard gradient.

b) 2-Chloro-4-({1-[(3,4-dihydroxycyclopentyl)methyl]piperidin-4-yl}oxy)-3-methylbenzonitrile

2-Chloro-4-{[1-(cyclopent-3-en-1-ylmethyl)piperidin-4-yl]oxy}-3-methylbenzonitrile (1.5 g), potassium osmate dihydrate (0.042 g) and N-methyl morpholine-N-oxide (50% solution in water, 3.2 mL) were stirred in a mixture of acetone (40 mL) and water (5 mL) then heated under reflux for 1h. The reaction mixture was allowed to cool to room temperature and a saturated solution of sodium metabisulfite in water was added. Product was extracted with dichloromethane. The aqueous fraction was basified by addition of a saturated solution of sodium bicarbonate in water and this was also extracted with dichloromethane. The dichloromethane fractions were combined and concentrated under reduced pressure. Crude material was purified using SCX resin. Non-basic impurities were washed off the column with a 1:1 mixture of methanol and dichloromethane then product was eluted with 10% aqueous ammonia in methanol. Solvent was removed under reduced pressure to give the subtitle compound as a solid, (1.3 g).

^{1}H NMR $\delta_{(CDCL3)}$ 1.42 - 1.64 (2H, m), 1.78 - 2.14 (4H, m), 2.23 - 2.47 (9H, m), 2.51 - 2.86 (4H, m), 3.72 (1H, t), 3.92 - 4.18 (2H, m), 4.38 - 4.50 (1H, m), 6.78 (1H, d), 7.46 (1H, d); MS: 365/367 $[M+H]^+$; Retention time: 1.53 min on standard gradient.

Intermediate 8

This illustrates the preparation of 4-[4-(3,4-dichloro-phenoxy)-piperidin-1-ylmethyl]-cyclopentane-1,2-diol which was prepared following the method of WO2004029041 using 4-(3,4-dichloro-2-ethylphenoxy)piperidine.

MS 360/362 ES+

Retention time standard 1.95

Intermediate 9

This illustrates the preparation of methyl (2*R*)-2-(3-nitrophenoxy)propanoate

3-Nitrophenol (3.7 g), triphenylphosphine (7.7 g) and methyl (2*S*)-2-hydroxypropanoate (2.5 mL) were added to tetrahydrofuran (30 mL) and the mixture was stirred at room temperature until a solution formed. The reaction mixture was cooled to 0 °C and diisopropylazodicarboxylate (5.8 mL) was added. After 0.5 h the reaction mixture was allowed to reach room temperature and stirring continued, under nitrogen, overnight. The reaction mixture was concentrated under reduced pressure and the resultant yellow oil was stirred in a 1:1 mixture of diethyl ether and *iso*-hexane. A white solid,

triphenylphosphine oxide, precipitated and was removed by filtration. The filtrate was concentrated under reduced pressure and the crude residue was purified by flash chromatography, eluting with 10% ethyl acetate in *iso*-hexane. This gave the title compound as a solid (5.7 g).

^{1}H NMR $\delta_{(CDCL3)}$ 1.67 (3H, dd), 3.79 (3H, d), 4.86 (1H, q), 7.21 (1H, dd), 7.44 (1H, td), 7.70 (1H, t), 7.84 - 7.87 (1H, m); Retention time: 1.92 min on standard gradient.

Intermediate 10

This illustrates the preparation of methyl (2*R*)-2-(3-aminophenoxy)propanoate

Methyl (2*R*)-2-(3-nitrophenoxy)propanoate (2.5 g) was dissolved in ethanol (25 mL) and powdered iron (3.1 g) was added. Ammonium chloride (3 g) was dissolved in the minimum amount of water possible and the solution was added to the reaction mixture. The mixture was heated, under reflux, overnight then allowed to cool to room temperature. Solid material was removed by filtration and the filtrate was concentrated under reduced pressure. Crude material was purified using SCX resin. Non-basic impurities were washed off the column with methanol and then product was eluted with 10% ammonia in methanol. Solvent was removed under reduced pressure to give a light brown oil (1.58 g) which was shown by LC/MS to be a mixture of the desired methyl ester and some ethyl ester.

^{1}H NMR $\delta_{(CDCL3)}$ methyl ester 1.59 (3H, dd), 3.48 (2H, s), 3.78 (3H, s), 4.68 - 4.76 (1H, m), 6.22 - 6.34 (3H, m), 7.03 (1H, t); MS methyl ester: 196 $[M+H]^+$.

Retention time: 1.25 min on standard gradient (methyl ester); 1.53 min on standard gradient (ethyl ester)

Intermediate 11

This illustrates the preparation of (4-chloro-2-nitro-phenoxy)-acetic acid *tert*-butyl ester

To a solution of 4-chloro-2-nitrophenol (2 g) in DMF (10 mL) was added potassium carbonate (1.59 g) and *t*-butyl bromoacetate (2.25 g). The mixture was heated to 70 °C. After 1h the reaction was partitioned between ether and water, and the organics were washed with brine, dried over sodium sulfate and concentrated in vacuo to give the title compound as a golden oil (3.1 g).

^{1}H NMR $\delta_{(DMSO)}$ 8.04 (d, 1H), 7.71 (dd, 1H), 7.31 (d, 1H), 4.92 (s, 2H), 1.40 (s, 9H).

Intermediate 12

This illustrates the preparation of 2-amino-4-chloro-phenoxy)-acetic acid *tert*-butyl ester

A solution of (4-chloro-2-nitro-phenoxy)-acetic acid *tert*-butyl ester (1.9 g) in ethanol (20 mL) with 5% platinum on carbon (0.2 g) was stirred at 3 Bar hydrogen pressure for 3 hours. Filtration of the solution, and concentration in vacuo gave the title compound (1.4 g) as a clear oil.

^{1}H NMR $\delta_{(DMSO)}$ 6.68 (d, 1H), 6.67 (d, 2H), 6.48 (dd, 1H), 4.60 (s, 2H), 1.43 (s, 9H).

EXAMPLE 1

This Example illustrates the preparation of methyl [3-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenyl]acetate

4-(3,4-Dichlorophenoxy)-1-(piperidin-4-ylmethyl)piperidine (0.7 g), methyl (3-bromophenyl)acetate (0.5 g), copper iodide (38 mg), L-proline (23 mg) and K_2CO_3 (0.8 g) were suspended in DMSO and heated to 85 °C for 16 h. The mixture was diluted with water and then extracted using EtOAc (3x 100 mL). The organic layers were combined, washed with brine, dried and the solvents were evaporated. The residue was purified by chromatography (EtOAc) to give the title compound (0.19 g), HPLC Ret. standard 2.98, MS (ES+) 491/493 $(M+H)^+$.

Examples 2 to 8 and13 (Table I below) were prepared by the same method as Example 1 using the appropriate aryl bromide or iodide.

EXAMPLE 9

This Example illustrates the preparation of methyl (2*R*)-2-[2-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenoxy]propanoate

2-(4-{[4-(3,4-Dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenol (100 mg) and K_2CO_3 (44 mg) were suspended in DMF (3 mL) and stirred for 15 min. Methyl (2*S*)-2-{[(4-methylphenyl)sulfonyl]oxy}propanoate (65 mg) was added and the reaction

mixture was heated to 65 °C for 18 h. The mixture was diluted with water and then extracted using TBME (3x 20 mL). The organic layers were combined, washed with bicarbonate solution, dried and the solvents were evaporated. The residue was purified by RPHPLC (gradient 75% - 5% aqueous ammonium acetate, 25% - 95% acetonitrile) to give the subtitle compound (100 mg), HPLC Ret. standard 3.28, MS (ES+ve) 521/523 $(M+H)^+$.

Examples 10 to 12 (Table I below) were prepared by the same method as Example 9 using the appropriate phenol and tosylate.

EXAMPLE 14

This Example illustrates the preparation of methyl [4-(4-{[4-(3,4-dichloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenyl]acetate

4-(3,4-Dichloro-2-methylphenoxy)-1-(piperidin-4-ylmethyl)piperidine (200 mg), methyl (4-bromophenyl)acetate (128 mg), Cs_2CO_3 (273 mg), palladium acetate (5 mg) and dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphone (12 mg) were combined and purged with nitrogen for 3 min. The reaction mixture was suspended in toluene (3 mL) and heated to 100 °C for 16 h. The mixture was diluted with water and then extracted using EtOAc (3x 100 mL). The organic layers were combined, washed with H_2O, dried and the solvents were evaporated. The residue was purified by chromatography (iso-hexane/EtOAc, 1/1 to neat EtOAc) to give the title compound (210 mg), HPLC Ret. standard. 3.04, MS (ES+ve) 505/507 $(M+H)^+$.

Examples 15 & 16 (Table I below) were prepared by the same method as Example 14 using the appropriate aryl bromide and amine.

EXAMPLE 17

This Example illustrates the preparation of methyl [4-(4-{[4-(3-chloro-4-cyano-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenyl]acetate

2-Chloro-4-({1-[(3,4-dihydroxycyclopentyl)methyl]piperidin-4-yl}oxy)-3-methylbenzonitrile (0.4 g) was stirred in a mixture of acetic acid (0.06 mL) and water (15 mL) until it dissolved. Sodium periodate (0.24 g) was added and stirring continued for 15 min. The reaction mixture was neutralised by addition of potassium carbonate (0.2 g) and the intermediate dialdehyde was extracted with dichloromethane. The dichloromethane

was washed with brine, dried ($MgSO_4$) and filtered into a flask containing: methyl (4-aminophenyl)acetate hydrochloride (0.22 g), triethylamine (0.15 mL), sodium triacetoxyborohydride (0.53 g) and acetic acid (0.06 mL) in dichloromethane (10 mL). The mixture was stirred, under nitrogen, for 1h. A saturated solution of sodium bicarbonate in water was added and product was extracted with dichloromethane. The dichloromethane was washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Crude material was purified by flash chromatography eluting with ethyl acetate. This gave the title compound as an oil, (0.24 g).

^{1}H NMR $\delta_{(CD3OD)}$ 1.27 - 1.45 (2H, m), 1.65 - 1.79 (1H, m), 1.81 - 1.96 (4H, m), 2.01 - 2.13 (2H, m), 2.29 - 2.36 (5H, m), 2.39 - 2.50 (2H, m), 2.63 - 2.78 (4H, m), 3.56 (2H, s), 3.62 - 3.70 (5H, m), 4.58 - 4.68 (1H, m), 6.96 (2H, d), 7.07 - 7.18 (3H, m), 7.62 (1H, d); MS: 496/498 $[M+H]^+$, Retention time: 2.65 min on standard gradient.

Examples 18 – 19 below were prepared from the appropriate diol (intermediate 7 or WO2004029041) and the appropriate amine

TABLE I

Example	Name	MS $[M+H]^+$ (ES+)	Retention time gradient
2	Methyl [2-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenyl]acetate	491/493	2.95 standard
3	Methyl [4-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenyl]acetate	491/493	1.21 fast
4	Methyl [3-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-4-methoxyphenyl]acetate	521/523	2.77 standard
5	*tert*-Butyl [2-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenoxy]acetate	549/551	2.66 fast
6	*tert*-Butyl [3-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenoxy]acetate	549/551	2.48 fast

7	*tert*-Butyl [4-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenoxy]acetate	549/551	1.95 fast
8	*tert*-Butyl 2-[2-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenoxy]-2-methylpropanoate	577/579	3.01 fast
10	Methyl (2*S*)-2-[2-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenoxy]propanoate	521/523	3.17 standard
11	Methyl (2*R*)-2-[3-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenoxy]propanoate	521/523	3.15 standard
12	Methyl (2*S*)-2-[3-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenoxy]propanoate	521/523	3.10 standard
13	Methyl 3-[2-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenyl]propanoate	505/507	3.01 standard
15	Methyl [4-(4-{[4-(2,4-dichloro-3-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenyl]acetate	505/507	2.98 standard
16	Methyl [3-(4-{[4-(2,4-dichloro-3-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenyl]acetate	505/507	3.03 standard
18	Methyl (2*R*)-2-[3-(4-{[4-(3-chloro-4-cyano-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenoxy]propanoate plus ethyl ester ^{1}H NMR (methyl ester) $\delta_{(CD3OD)}$ 1.23 - 1.43 (2H, m), 1.56 (3H, d), 1.65 - 1.80 (1H, m), 1.82 - 1.94 (4H, m), 2.02 - 2.13 (3H, m), 2.29 - 2.36 (5H, m), 2.39 - 2.51 (2H, m), 2.64 - 2.78 (4H, m), 3.67 (2H, d), 3.75 (3H, s), 4.59 - 4.68 (1H, m), 6.34 (1H, dd),	526/528	1.55 fast (methyl ester) 1.78 (ethyl ester)

	6.52 (1H, t), 6.63 (1H, dd), 7.07 - 7.16 (2H, m), 7.61 (1H, d)		
19	Methyl (3-{4-[4-(3,4-dichloro-2-ethyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-phenyl)-acetate	519/521	2.39 fast

EXAMPLE 20

This Example illustrates the preparation of [3-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenyl]acetic acid

Methyl [3-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenyl]acetate (0.19 g) was suspended in MeOH/H_2O (4/1, 5mL) and LiOH (25mg) was added. The mixture was heated to 85 °C for 2h. The reaction was allowed to cool and the solvents were evaporated. The residue was dissolved in MeOH and acidified with AcOH and then purified by RPHPLC (gradient 95% - 50% aqueous ammonium acetate, 5% - 50% acetonitrile) to give the title compound (76 mg), HPLC Ret. fast 0.42, MS (ES+) 477/479 $(M+H)^+$.

^{1}H NMR $\delta_{(CD3OD+NaOD)}$ 1.28 - 1.40 (2H, m), 1.63 - 1.82 (3H, m), 1.82 - 1.91 (2H, m), 1.96 - 2.05 (2H, m), 2.25 - 2.37 (4H, m), 2.62 - 2.78 (4H, m), 3.42 (2H, s), 3.62 - 3.68 (2H, m), 4.35 - 4.43 (1H, m), 6.79 - 6.84 (2H, m), 6.89 (1H, dd), 6.98 - 7.01 (1H, m), 7.08 - 7.14 (2H, m), 7.37 (1H, d).

Examples 21 to 23 and 27 to 38 (Table II below) were prepared by the same method as Example 16.

EXAMPLE 24

This Example illustrates the preparation of [2-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenoxy]acetic acid

tert-Butyl [2-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenoxy]acetate (0.11 g) was dissolved in dichloromethane (5 mL) and TFA (5 mL) was added. The solution was stirred at RT for 16 h. The solvents were evaporated. The residue was dissolved in MeOH and then purified by RPHPLC (gradient 95% - 50% aqueous ammonium acetate, 5% - 50% acetonitrile) to give the title compound (64 mg), HPLC Ret. fast 0.50, MS (ES+ve) 493/495 $(M+H)^+$.

^{1}H NMR $\delta_{(CD3OD+NaOD)}$ 1.38 - 1.50 (2H, m), 1.63 - 1.88 (5H, m), 1.96 - 2.04 (2H, m), 2.26 - 2.37 (4H, m), 2.53 - 2.62 (2H, m), 2.70 - 2.78 (2H, m), 3.50 - 3.57 (2H, m), 4.35 - 4.43 (1H, m), 4.45 (2H, s), 6.83 - 6.94 (4H, m), 6.95 - 6.99 (1H, m), 7.09 (1H, d), 7.37 (1H, d).

Examples 25 and 26 (Table II below) were prepared by the same method as Example 20. Example 39 was prepared by the method of Example 20 from an ester prepared by the method of Example 17.

EXAMPLE 40

This Example illustrates the preparation of (2-chloro-6-{4-[4-(3,4-dichloro-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-phenoxy)-acetic acid

To a solution of 4-[4-(3,4-dichloro-phenoxy)-piperidin-1-ylmethyl]-cyclopentane-1,2-diol (0.54 g) in dichloromethane (20 mL), was added lead tetraacetate (0.99 g) and potassium carbonate (0.25 g). The mixture was stired at room temperature for 1.5 h, then 3-chloro-2-methoxy-aniline (0.26 g) and sodium triacetoxyborohydride (0.64 g) were added. After a further 2 h the mixture was partitioned between dichloromethane and sodium hydrogen carbonate solution (sat.) and the organics were dried over sodium sulfate. Concentration in vacuo gave a brown gum, that was taken up in dichloromethane (20 mL) and treated dropwise with boron tribromide (1.0 M soln in dichloromethane, 12.4 mL) and stirred at RT for 1 h. The reaction was diluted with methanol (100 mL) and concentrated in vacuo. The residue was partitioned between ethyl acetate and sodium hydrogen carbonate solution (sat.) and the organics were dried over sodium sulfate and concentrated in vacuo. The residue was subject to reversed phase HPLC (Xterra column, eluting 50% to 95% acetonitrile in aqueous ammonia (0.2%)), yielding 2-chloro-6-{4-[4-(3,4-dichloro-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-phenol (0.12 g). The phenol was dissolved in DMF (5 mL); potassium carbonate (0.03 g) and methyl bromoacetate (0.15 g) were added. The reaction was heated at 70 °C for 2 h and then partitioned between sodium hydrogen carbonate solution (sat.) and diethylether. The organics were dried over sodium sulfate and concentrated in vacuo. The residue was dissolved in THF:water (1:1, 5 mL) and lithium hydroxide (0.02 g) was added. The reaction was stirred at RT for 1 hr and then concentrated in vacuo. The residue was dissolved in water (5 mL) and neutralised with the

dropwise addition of HCl (1 M) to precipitate the title compound (0.03 g) as a white solid which was collected by filtration.

^{1}H NMR $\delta_{(DMSO)}$ 7.50 (d, 1H), 7.26 (d, 1H), 7.14 - 6.95 (m, 4H), 4.57 (s, 2H), 4.49 - 4.39 (m, 1H), 2.75 - 2.55 (m, 2H), 2.49 - 2.36 (m, 2H), 2.29 - 2.16 (m, 4H), 2.00 - 1.87 (m, 2H), 1.86 - 1.73 (m, 2H), 1.67 - 1.54 (m, 2H), 1.32 - 1.14 (m, 2H), 3.57 - 3.13 (m, 3H); MS [M-H]-=525/527 (APCI-).

Examples 41 – 43 (Table II below) were prepared by the same method as Example 40. Examples 44 & 45 were prepared by similar methodology to the above compounds.

TABLE II

Example	Name	MS $[M+H]^+$ (ES+)	Retention time gradient	^{1}H NMR
21	[2-(4-{[4-(3,4-Dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenyl]acetic acid	477/479	0.59 fast	$\delta_{(CD3OD+NaOD)}$ 1.37 - 1.50 (2H, m), 1.55 - 1.69 (1H, m), 1.71 - 1.86 (4H, m), 1.97 - 2.06 (2H, m), 2.28 - 2.38 (4H, m), 2.60 - 2.68 (2H, m), 2.70 - 2.80 (2H, m), 3.07 - 3.14 (2H, m), 3.62 (2H, s), 4.35 - 4.43 (1H, m), 6.89 (1H, dd), 6.94 - 6.99 (1H, m), 7.04 - 7.07 (1H, m), 7.09 - 7.14 (2H, m), 7.25 - 7.29 (1H, m), 7.37 (1H, d)
22	[4-(4-{[4-(3,4-Dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenyl]acetic acid	477/479	1.82 standard	$\delta_{(CD3OD+NaOD)}$ 1.30 - 1.45 (2H, m), 1.60 - 1.94 (5H, m), 1.97 - 2.08 (2H, m), 2.27 - 2.41 (4H, m), 2.61 - 2.82 (4H, m), 3.40 (2H, s), 3.57 - 3.65 (2H, m), 4.37 - 4.46 (1H, m), 6.88 - 6.97 (3H, m), 7.11 - 7.14 (1H, m), 7.19 - 7.24 (2H, m), 7.37 - 7.42 (1H, m)
23	[3-(4-{[4-(3,4-Dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-4-methoxyphenyl]acetic acid	507/509	2.40 NH4/85/30/A/5	$\delta_{(CD3OD+NaOD)}$ 1.27 - 1.48 (2H, m), 1.61 - 1.89 (5H, m), 1.96 - 2.06 (2H, m), 2.26 - 2.39 (4H, m), 2.53 - 2.62 (2H, m), 2.70 - 2.79 (2H, m), 3.36 - 3.44 (4H, m), 3.83 (3H, s), 4.36 - 4.43 (1H, m), 6.83 (1H, d), 6.89 (1H, dd), 6.93 - 6.96 (1H, m), 7.01 (1H, d), 7.10 (1H, d), 7.37 (1H, d)

25	[3-(4-{[4-(3,4-Dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenoxy]acetic acid	493/495	1.66 standard	$\delta_{(CD3OD+NaOD)}$ 1.28 - 1.44 (2H, m), 1.60 - 1.93 (5H, m), 1.98 - 2.10 (2H, m), 2.26 - 2.41 (4H, m), 2.63 - 2.81 (4H, m), 3.64 - 3.71 (2H, m), 4.36 (2H, s), 4.37 - 4.46 (1H, m), 6.41 - 6.46 (1H, m), 6.56 - 6.63 (2H, m), 6.91 (1H, dd), 7.04 - 7.19 (2H, m), 7.40 (1H, d)
26	[4-(4-{[4-(3,4-Dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenoxy]acetic acid	493/495	0.60 fast	$\delta_{(CD3OD+NaOD)}$ 1.31 - 1.46 (2H, m), 1.59 - 1.95 (5H, m), 1.97 - 2.08 (2H, m), 2.28 - 2.40 (4H, m), 2.57 - 2.68 (2H, m), 2.71 - 2.81 (2H, m), 3.44 - 3.52 (2H, m), 4.33 (2H, s), 4.37 - 4.46 (1H, m), 6.86 - 6.93 (3H, m), 6.95 - 7.01 (2H, m), 7.12 (1H, d), 7.40 (1H, d)
27	2-[2-(4-{[4-(3,4-Dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenoxy]-2-methylpropanoic acid	521/523	0.61 fast	$\delta_{(CD3OD+NaOD)}$ 1.38 - 1.48 (2H, m), 1.54 (6H, s), 1.64 - 1.88 (5H, m), 1.97 - 2.05 (2H, m), 2.28 - 2.38 (4H, m), 2.51 - 2.59 (2H, m), 2.70 - 2.79 (2H, m), 3.51 - 3.58 (2H, m), 4.36 - 4.43 (1H, m), 6.78 - 6.84 (2H, m), 6.87 - 6.96 (3H, m), 7.10 (1H, d), 7.38 (1H, d)
28	(2*R*)-2-[2-(4-{[4-(3,4-Dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenoxy]propanoic acid	507/509	1.66 standard	$\delta_{(CD3OD+NaOD)}$ 1.28 - 1.50 (2H, m), 1.56 (3H, s), 1.59 - 1.90 (5H, m), 1.97 - 2.06 (2H, m), 2.28 - 2.38 (4H, m), 2.42 - 2.51 (1H, m), 2.62 - 2.70 (1H, m), 2.71 - 2.79 (2H, m), 3.35 - 3.42 (1H, m), 3.76 - 3.83 (1H, m), 4.36 - 4.43 (1H, m), 4.53 (1H, q), 6.80 - 6.96 (5H, m), 7.10 (1H, d), 7.37 (1H, d)

29	(2*S*)-2-[2-(4-{[4-(3,4-Dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenoxy]propanoic acid	507/509	1.60 standard	$\delta_{(CD3OD+NaOD)}$ 1.27 - 1.48 (2H, m), 1.56 (3H, d), 1.60 - 1.90 (5H, m), 1.96 - 2.05 (2H, m), 2.27 - 2.38 (4H, m), 2.43 - 2.51 (1H, m), 2.62 - 2.71 (1H, m), 2.71 - 2.79 (2H, m), 3.35 - 3.42 (1H, m), 3.76 - 3.83 (1H, m), 4.36 - 4.43 (1H, m), 4.53 (1H, q), 6.80 - 6.91 (4H, m), 6.92 - 6.95 (1H, m), 7.10 (1H, d), 7.37 (1H, d)
30	(2*R*)-2-[3-(4-{[4-(3,4-Dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenoxy]propanoic acid	507/509	1.51 standard	$\delta_{(CD3OD+NaOD)}$ 1.26 - 1.40 (2H, m), 1.50 (3H, d), 1.63 - 1.90 (5H, m), 1.96 - 2.05 (2H, m), 2.24 - 2.38 (4H, m), 2.60 - 2.78 (4H, m), 3.59 - 3.67 (2H, m), 4.35 - 4.43 (1H, m), 4.47 (1H, q), 6.37 - 6.41 (1H, m), 6.51 - 6.56 (2H, m), 6.89 (1H, dd), 7.06 (1H, t), 7.09 (1H, d), 7.37 (1H, d)
31	(2*S*)-2-[3-(4-{[4-(3,4-Dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenoxy]propanoic acid	507/509	1.50 standard	$\delta_{(CD3OD)}$ 1.26 - 1.40 (3H, m), 1.50 (3H, d), 1.63 - 1.90 (5H, m), 1.96 - 2.05 (2H, m), 2.24 - 2.37 (4H, m), 2.61 - 2.69 (2H, m), 2.70 - 2.77 (2H, m), 3.60 - 3.66 (2H, m), 4.35 - 4.42 (1H, m), 6.37 - 6.41 (1H, m), 6.51 - 6.56 (2H, m), 6.89 (1H, dd), 7.05 (1H, t), 7.09 (1H, d), 7.37 (1H, d)
32	3-[2-(4-{[4-(3,4-Dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenyl]propanoic acid	491/493	1.95 standard	$\delta_{(CD3OD+NaOD)}$ 1.26 - 1.50 (2H, m), 1.59 - 1.87 (5H, m), 1.96 - 2.06 (2H, m), 2.27 - 2.40 (4H, m), 2.42 - 2.50 (2H, m), 2.61 - 2.79 (4H, m), 2.93 - 3.00 (2H, m), 3.01 - 3.07 (2H, m), 4.36 - 4.44 (1H, m), 6.89 (1H, dd), 6.93 - 6.98 (1H, m), 7.06 - 7.11 (3H, m), 7.21 (1H, d), 7.38 (1H, d)

33	[4-(4-{[4-(3,4-Dichloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenyl]acetic acid	491/493	1.71 standard	$\delta_{(CD3OD+NaOD)}$ 1.28 - 1.46 (2H, m), 1.61 - 1.96 (5H, m), 1.97 - 2.11 (2H, m), 2.23 - 2.47 (4H, m), 2.34 (3H, s), 2.60 - 2.78 (4H, m), 3.40 (2H, s), 3.56 - 3.65 (2H, m), 4.41 - 4.50 (1H, m), 6.89 - 7.00 (3H, m), 7.18 - 7.34 (3H, m)
34	[4-(4-{[4-(2,4-Dichloro-3-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenyl]acetic acid	491/493	1.65 standard	$\delta_{(CD3OD+NaOD)}$ 1.29 - 1.46 (2H, m), 1.63 - 1.78 (1H, m), 1.80 - 1.95 (4H, m), 1.96 - 2.09 (2H, m), 2.26 - 2.34 (2H, m), 2.36 - 2.45 (2H, m), 2.47 (3H, s), 2.59 - 2.81 (4H, m), 3.40 (2H, s), 3.52 - 3.70 (2H, m), 4.43 - 4.56 (1H, m), 6.89 - 7.03 (3H, m), 7.16 - 7.33 (3H, m)
35	[3-(4-{[4-(2,4-Dichloro-3-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenyl]acetic acid	491/493	1.65 standard	$\delta_{(CD3OD+NaOD)}$ 1.29 - 1.44 (2H, m), 1.63 - 1.78 (1H, m), 1.80 - 1.95 (4H, m), 1.96 - 2.09 (2H, m), 2.28 - 2.33 (2H, m), 2.34 - 2.45 (2H, m), 2.47 (3H, s), 2.63 - 2.81 (4H, m), 3.44 (2H, s), 3.63 - 3.72 (2H, m), 4.44 - 4.53 (1H, m), 6.81 - 6.87 (2H, m), 6.97 (1H, d), 7.00 - 7.03 (1H, m), 7.14 (1H, t), 7.28 (1H, d)
36	[4-(4-{[4-(3-Chloro-4-cyano-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenyl]acetic acid	482/484		$\delta_{(CD3OD)}$ 1.29 - 1.41 (2H, m), 1.62 - 1.75 (1H, m), 1.80 - 1.90 (4H, m), 2.01 - 2.09 (2H, m), 2.28 (2H, d), 2.31 (3H, s), 2.37 - 2.46 (2H, m), 2.60 - 2.72 (4H, m), 3.38 (2H, s), 3.58 (2H, d), 4.57 - 4.64 (1H, m), 6.92 (2H, d), 7.08 (1H, d), 7.19 (2H, d), 7.60 (1H, d)

37	(2*R*)-2-[3-(4-{[4-(3-Chloro-4-cyano-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenoxy]propanoic acid	512/514	1.33 standard	$\delta_{(CD3OD)}$ 1.28 - 1.43 (2H, m), 1.53 (3H, d), 1.64 - 1.77 (1H, m), 1.82 - 1.94 (4H, m), 2.02 - 2.13 (2H, m), 2.30 (2H, d), 2.34 (3H, s), 2.39 - 2.49 (2H, m), 2.63 - 2.77 (4H, m), 3.66 (2H, d), 4.49 (1H, q), 4.59 - 4.67 (1H, m), 6.40 - 6.43 (1H, m), 6.54 - 6.59 (2H, m), 7.08 (2H, t), 7.62 (1H, d)
38	(3-{4-[4-(3,4-Dichloro-2-ethyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-phenyl)-acetic acid	505/507	1.92 standard	$\delta_{(CD3OD)}$ 1.12 (3H, t), 1.27 - 1.41 (2H, m), 1.62 - 1.74 (1H, m), 1.77 - 1.91 (4H, m), 1.98 - 2.07 (2H, m), 2.25 - 2.29 (2H, m), 2.34 - 2.43 (2H, m), 2.62 - 2.75 (4H, m), 2.87 (2H, q), 3.41 (2H, s), 3.61 - 3.68 (2H, m), 4.42 - 4.48 (1H, m), 6.78 - 6.83 (2H, m), 6.91 (1H, d), 6.98 - 7.00 (1H, m), 7.11 (1H, t), 7.26 (1H, d)
39	(4-Chloro-2-{4-[4-(3,4-dichloro-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-phenoxy)-acetic acid hydrochloride	529/531		$\delta_{(DMSO)}$ 7.59 - 7.52 (m, 1H), 7.40 - 7.33 (m, 1H), 7.11 - 7.00 (m, 1H), 6.97 - 6.91 (m, 1H), 6.90 - 6.81 (m, 2H), 4.69 (s, 2H), 4.66 - 4.58 (m, 3H), 3.64 - 2.99 (m, 7H), 2.72 - 1.82 (m, 8H), 1.49 - 1.32 (m, 2H)
41	[2-(4-{[4-(2,4-dichloro-3-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-4-methylphenoxy]acetic acid	525/527 (APCI-)		$\delta_{(DMSO)}$ 7.50 (d, 1H), 7.26 (d, 1H), 6.98 (dd, 1H), 6.94 - 6.86 (m, 2H), 6.83 (s, 1H), 4.65 (s, 2H), 4.45 (s, 1H), 3.45 - 3.35 (m, 2H), 2.72 - 2.63 (m, 2H), 2.58 - 2.50 (m, 2H), 2.25 - 2.19 (m, 4H), 1.97 - 1.88 (m, 2H), 1.80 - 1.71 (m, 2H), 1.68 - 1.53 (m,

				3H), 1.33 - 1.17 (m, 2H)
42	[2-(4-{[4-(2,4-dichloro-3-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-4-methylphenoxy]acetic acid	522/524		$\delta_{(DMSO)}$ 1.2-1.4 (m, 2H), 1.55-1.8 (m, 5H), 1.8-2.0 (m, 2H), 2.21 (s, 3H), 2.40 (s, 3H), 2.1-2.8 (m, 7H), 3.08 (s, H), 3.3-3.5 (m, 2H), 4.4-4.6 (m, H), 4.57 (s, 2H), 6.85-6.60 (m, 3H), 7.12 (d, H), 7.34 (d, H)
43	[2-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-4-methylphenoxy]acetic acid acetate	522/524		$\delta_{(DMSO)}$ 1.2-1.3 (m, 3H), 1.36 (d, 3H), 1.5-1.7 (m, 4H), 1.7-1.8 (m, 2H), 1.91 (s, 3H), 1.9-2.0 (m, 2H), 2.18 (s, 3H, AcOH), 2.1-2.22 (s, 2H), 2.40 (dd, 2H), 2.6-2.7 (m, 2H), 3.35 (d, H), 3.62 (d, H), 4.25 (q, H), 4.4-4.5 (m, H), 6.58 (s, 2H), 6.61 (s, H), 6.98 (dd, H), 7.26 (d, H), 7.50 (d, H)
44	(2*S*)-2-[3-(4-{[4-(3,4-dichloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenoxy]propanoic acid	$(M-H)^-$ 519/521/523 (APCI -)		$\delta_{(CD3OD)}$ 1.30 – 1.42 (2H, m), 1.54 (3H, d), 1.67 – 1.79 (1H, m), 1.80 – 1.95 (4H, m), 2.06 (2H, d), 2.31 (2H, d), 2,35 (3H, s), 2.41 (2H, s), 2.69 (4H, t), 2.67 (2H, d), 4.43 – 4.55 (2H, m), 6.41 – 6.45 (1H, m), 6.56 – 6.61 (2H, m), 6.96 (1H, d), 7.10 (1H, t), 7.31 (1H, d).
45	[3-(4-{[4-(3,4-dichloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)phenyl]acetic acid	$(M-H)^-$ 489/491/493 (APCI -)		$\delta_{(CD3OD)}$ 1.35 (1H, ddd), 1.62 – 1.75 (1H, m), 1.76 – 1.91 (4H, m), 1.97 – 2.06 (2H, m), 2.27 (2H, d), 2.31 (3H, s), 2.33 – 2.42 (2H, m), 2.61 – 2.75 (4H, m), 3.42 (2H, s), 3.65 (2H, d), 4.39 – 4.47 (1H, m), 6.80 (1H, s), 6.82 (1H, s), 6.91 (1H, d), 6.98 (1H, s), 7.12 (1H, t), 7.27 (1H, d).

EXAMPLE 46

Pharmacological Analysis: Calcium flux $[Ca^{2+}]_i$ assay

Human eosinophils

Human eosinophils were isolated from EDTA anticoagulated peripheral blood as previously described (Hansel et al., *J. Immunol. Methods*, 1991, 145, 105-110). The cells were resuspended ($5x10^6$ mL^{-1}) and loaded with 5μM FLUO-3/AM + Pluronic F127 2.2μl/mL (Molecular Probes) in low potassium solution (LKS; NaCl 118mM, $MgSO_4$ 0.8mM, glucose 5.5mM, Na_2CO_3 8.5mM, KCl 5mM, HEPES 20mM, $CaCl_2$ 1.8mM, BSA 0.1%, pH 7.4) for one hour at room temperature. After loading, cells were centrifuged at 200g for 5min and resuspended in LKS at $2.5x10^6$ mL^{-1}. The cells were then transferred to 96 well FLIPr plates (Poly-D-Lysine plates from Becton Dickinson pre-incubated with 5μM fibronectin for two hours) at 25μl/well. The plate was centrifuged at 200g for 5min and the cells were washed twice with LKS (200μl; room temperature).

A compound of the Examples was pre-dissolved in DMSO and added to a final concentration of 0.1%(v/v) DMSO. Assays were initiated by the addition of an A_{50} concentration of eotaxin and the transient increase in fluo-3 fluorescence (l_{Ex} =490nm and l_{Em} = 520nm) monitored using a FLIPR (Fluorometric Imaging Plate Reader, Molecular Devices, Sunnyvale, U.S.A.).

Compounds of the Examples were found to be antagonists if the increase in fluorescence induced by eotaxin (a selective CCR3 agonist) was inhibited in a concentration dependent manner. The concentration of antagonist required to inhibit the fluorescence by 50% can be used to determine the IC_{50} for the antagonist at the CCR3 receptor.

EXAMPLE 47

Human eosinophil chemotaxis

Human eosinophils were isolated from EDTA anticoagulated peripheral blood as previously described (Hansel et al., *J. Immunol. Methods*, 1991, 145, 105-110). The cells were resuspended at $10x10^6$ mL^{-1} in RPMI containing 200 IU/mL penicillin, 200 μg/mL streptomycin sulfate and supplemented with 10% HIFCS, at room temperature.

Eosinophils (700 μl) were pre-incubated for 15 mins at 37° C with 7 μl of either vehicle or compound (100x required final concentration in 10% DMSO). The chemotaxis

plate (ChemoTx, 3μm pore, Neuroprobe) was loaded by adding 28μl of a concentration of eotaxin 0.1 to 100nM (a selective CCR3 agonist over this concentration range) containing a concentration of a compound according to the Examples or solvent to the lower wells of the chemotaxis plate. The filter was then placed over the wells and 25 μl of eosinophil suspension were added to the top of the filter. The plate was incubated for 1 hr at 37° C in a humidified incubator with a 95% air/5% CO_2 atmosphere to allow chemotaxis.

The medium, containing cells that had not migrated, was carefully aspirated from above the filter and discarded. The filter was washed once with phosphate buffered saline (PBS) containing 5 mM EDTA to remove any adherent cells. Cells that had migrated through the filter were pelleted by centrifugation (300xg for 5 mins at room temperature) and the filter removed and the supernatant transferred to each well of a 96-well plate (Costar). The pelleted cells were lysed by the addition of 28 μl of PBS containing 0.5% Triton x100 followed by two cycles of freeze/thawing. The cell lysate was then added to the supernatant. The number of eosinophils migrating was quantified according to the method of Strath et al., *J. Immunol. Methods*, 1985, 83, 209 by measuring eosinophil peroxidase activity in the supernatant.

Compounds of the Examples were found to be antagonists of eotaxin mediated human eosinophil chemotaxis if the concentration response to eotaxin was shifted to the right of the control curve. Measuring the concentration of eotaxin required to give 50% chemotaxis in the presence or absence of compounds enables the apparent affinity of the compounds at CCR3 to be calculated.

EXAMPLE 48

Guinea-pig isolated trachea

(See for example, Harrison, R.W.S., Carswell, H. & Young, J.M. (1984) European J. Pharmacol., 106, 405-409.)

Male albino Dunkin-Hartley guinea-pigs (250g) were killed by cervical dislocation and the whole trachea removed. After clearing the adherent connective tissue, the trachea was cut into six ring segments each three cartilage bands wide and then suspended in 20mL organ baths containing Krebs-Henseleit solution of the following composition (mM): NaCl 117.6, NaH_2PO_4 0.9, $NaHCO_3$ 25.0, $MgSO_4$ 1.2, KCl 5.4, $CaCl_2$ 2.6 and glucose 11.1. The buffer was maintained at 37°C and gassed with 5% CO_2 in oxygen. Indomethacin (2.8μM) was added to the Krebs solution to prevent development of smooth muscle tone due to the synthesis of cyclo-

oxygenase products. The tracheal rings were suspended between two parallel tungsten wire hooks, one attached to an Ormed beam isometric force transducer and the other to a stationary support in the organ bath. Changes in isometric force were recorded on 2-channel Sekonic flat bed chart recorders.

Experimental protocols

At the beginning of each experiment a force of 1g was applied to the tissues and this was reinstated over a 60 minute equilibration period until a steady resting tone was achieved. Subsequently, a cumulative histamine concentration effect (E/[A]) curve was constructed at 0.5 $\log_{10}$ unit increments, in each tissue. The tissues were then washed and approximately 30 minutes later, test compound or vehicle (20% DMSO) was added. Following an incubation period of 60 minutes a second E/[A] curve was performed to histamine.

Contraction responses were recorded as a percentage of the first curve maximum.

Data analysis

Experimental E/[A] curve data were analysed for the purposes of estimating the potencies ($p[A_{50}]$ values) of histamine in the absence and presence of the test compound. Affinity (pA_2) values of test compounds were subsequently calculated using the following equation:

$$\log(r-1) = \log[B] + pA_2$$

where $r = [A]_{50}$ in presence of test compound/$[A]_{50}$ in absence of antagonist and [B] is the concentration of test compound. Compounds of the Examples were found to be H1 antagonists.

EXAMPLE 49

Histamine H1 receptor binding activity of compounds of the invention was assessed by competition displacement of 1nM [3H]-pyrilamine (Amersham, Bucks, Product code TRK 608, specific activity 30Ci/mmol) to 2μg membranes prepared from recombinant CHO-K1 cells expressing the human H1 receptor (Euroscreen SA, Brussels, Belgium, product code ES-390-M) in assay buffer (50mM Tris pH 7.4 containing 2mM $MgCl_2$, 250mM sucrose and 100mM NaCl) for 1 hour at room temperature.

The following compounds of the invention gave inhibition of [3H] pyrilimine binding:

Example	H1 pKi /[1328_S]
20	8.3
21	7.8
22	7.8
23	7.9
24	7.8
25	8.3
26	7.4
27	7.5
28	8.0
29	7.9
30	7.9
33	7.9
37	6.4
39	8.7
40	8.5
43	7.8
44	7.7